COMMUNICATION

Facile sulfation of C_{60} using P_2O_5 as an oxidation promoter

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Reactivity of C_{60} molecules toward the oxidative sulfation reaction induced by H_2SO_4–SO_3 is highly enhanced by P_2O_5, leading to hexacyclosulfated fullerene intermediates which are converted to dodecahydroxyfullerenes upon hydrolysis.

The high chemical reactivity of C_{60} molecules has allowed the synthesis of an enormous number of fullerene derivatives suitable for materials and biological applications.[1,2] Among them, hydrophilic polyhydroxylated fullerenes (fullerenols)[3–5] were reported to exhibit the free-radical scavenging activities against reactive oxygen species (ROS) under physiological conditions.[6] Related therapeutic investigations of fullerenols included inhibition of H_2O_2-elicited oxidative damage of brain neurons,[7] removal of superoxide radicals in the whole blood associated with gastric cancer,[8] attenuation of exsanguination-induced bronchoconstriction,[9] and antiproliferation of the vascular smooth muscle cells.[10] In materials applications, fullerenols were utilized as a molecular core for the preparation of star-shaped polymers[11] and hypercrosslinked networks.[12]

One synthesis of fullerenols **1** was carried out by hydrolysis of polycyclosulfated fullerenes, which were products resulting from the reaction of C_{60} with oleum [H_2SO_4–SO_3 (28–30%)] at 60 °C for a period of 12 h to 3 d depending on the C_{60} *vs.* oleum ratio by weight used.[13] A slow dissolution of C_{60} into the acid medium in an over-saturated mixture can prevent the efficient oxidation of C_{60} and prolong the reaction period. We found that cyclosulfation of fullerene molecules, using oleum as an oxidative sulfation reagent, in a fully dissolved state can be greatly accelerated to completion within a reaction period of 80 min at 60 °C upon the addition of P_2O_5 (8.5 equiv.), as a secondary oxidation promoter. This reaction is both dose and temperature dependent. Thus, the period required for a complete reaction was shortened to 40 or 20 min when 17 or 34 equiv. of P_2O_5, respectively, was applied under similar reaction conditions. When the reaction temperature was increased to 80 °C with 17 equiv. of P_2O_5, complete sulfation was achieved within as short a time as 5–10 min.

Reaction of the fullerene molecules with oleum involved a SO_3-induced stoichiometric electron oxidation of C_{60} and its analogues, forming cationic radical intermediates of fullerenes which were stabilized under the strongly acidic conditions. Formation of these radicals can be readily followed by a visual change of the reaction mixture to a dark brownish-green solution, containing any suspended unreacted fullerene particles. Existence of the fullerenic radicals in solution was substantiated by detection of an absorption peak in the EPR spectrum.[14,15] The attack of the resulting cationic intermediates by nucleophilic anionic sulfate species, such as HSO_4^- and $HS_2O_7^-$ (as a product of HSO_4^- and SO_3), afforded the corresponding cyclosulfated fullerenes **2** which precipitated out from the acid solution as orange-red solids, as shown in Scheme 1. Removal of sulfuric acid was carried out by transferring the resulting acid suspension dropwise into a mixture of anhydrous diethyl ether and acetonitrile (1:2) to effect further precipitation of dissolved **2**. Hydrolysis of **2** in water at 85 °C gave fullerenols **1** in an overall yield of roughly 80–87% from C_{60}.

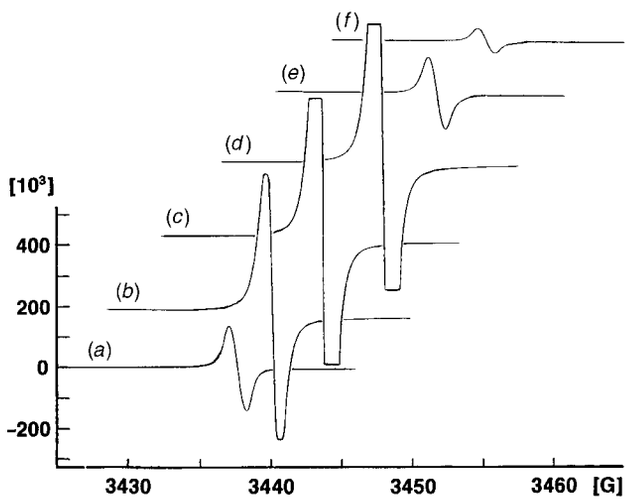
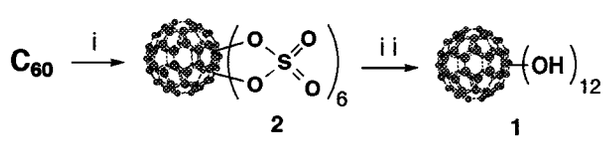


Fig. 1 Relative intensity of the EPR profiles induced by the reaction of C_{60} with H_2SO_4–SO_3 at a reaction period of (*a*) 0.0 min (control), (*b*) 5.0 min, (*c*) 1.7 h, (*d*) 2.8 h, (*e*) 12.0 h and (*f*) 40.0 h after the addition of P_2O_5 at ambient temperatures, showing the reactivity enhancement on the electron oxidation of C_{60} by P_2O_5



Scheme 1 *Reagents and conditions*: i, H_2SO_4–SO_3 (28–30%), P_2O_5 (13.0 equiv.), 60 °C, 1 h; ii, H_2O, 85 °C, 10 h

Effect of the reactivity enhancement on the electron oxidation of the C_{60} molecules by oxide promoters in the presence of oleum was investigated *via* changes of the integration intensity of an EPR band corresponding to the fullerenic radicals generated. A higher electron oxidation rate of C_{60} and its derivatives leads to a higher $S = 1/2$ EPR signal of the corresponding cationic radical intermediates. At the early stage of the reaction in fuming sulfuric acid, the initially formed cationic C_{60} products contain what are evidently ground-state triplet diradicals.[15a] Subsequent sulfation and further oxidation of these diradicals may produce even-numbered sulfate derivatives of C_{60} which are EPR silent species. Therefore, the observed peak intensity represents roughly 50% of the total sulfation sites on average. In the absence of a secondary oxidation promoter, the treatment of C_{60} (5 mg) with oleum (5 g) for a reaction period of 5 min at ambient temperatures[16] gave a greenish mixture showing a narrow EPR resonance resembling the profile reported previously[15b] [Fig. 1(*a*)]. Upon addition of P_2O_5 (250 mg, excess) and subsequent stirring of the resulting

mixture for an additional 5 min, a sharp increase of the total integrated EPR susceptibility by more than a factor of 8 was detected as shown in Fig. 1(*b*). This indicated a significant enhancement of the electron oxidation rate of C_{60} by P_2O_5, which served as a secondary oxidant. Intensity of the profile increased progressively by a factor of 43 and 75 while a maximum integrated EPR susceptibility was reached at a reaction period of 1.7 and 2.8 h as depicted in Fig. 1(*c*) and (*d*), respectively. Without P_2O_5, in a separate control experiment under similar reaction conditions for a period of 5 min to 2.5 h, the C_{60} molecules reacted with oleum to afford radical intermediates displaying a comparable EPR profile with a slow increase in intensity by a factor of less than 2–3 during the entire reaction period. Thus, comparison between these two experiments substantiated the inductive effect of P_2O_5 in enhancing the electron oxidation rate of C_{60}. As the reaction proceeded further to completion, the relative EPR intensity declined sharply to a minimum value at a reaction period of between 12 and 40 h, as shown in Fig. 1(*e*) and (*f*), respectively. The lack of fullerenic radicals in the end-products revealed their chemical composition as even-numbered sulfate derivatives of C_{60} (one cyclosulfate moiety is considered to consist of two sulfate functional groups). Hydrolysis of these sulfate derivatives should afford an even-numbered polyhydroxylated C_{60}.

Characteristics of fullerenic cyclosulfate moieties in **2** were noticed in that its infrared spectrum displayed two sharp, strong absorptions centered at 1426 and 1229 cm^{-1}, corresponding to the asymmetric RO–SO_2–OR stretch and symmetric RO–SO_2–OR stretch bands, respectively. Both the absorption intensity and the peak position of these two bands were found to agree well with those of $-SO_2-$ absorptions reported for polycyclosulfated C_{60} synthesized by the reaction of C_{60} with H_2SO_4–SO_3 in the absence of P_2O_5.[13] Hexacyclosulfated C_{60} **2** was readily hydrolyzable in H_2O at 85 °C to afford dodecahydroxylated fullerene **1**. In contrast, the hydrolysis rate of **2** at 0 °C was found to be very slow. Therefore, it is possible to apply ice–water for brief washings and removal of sulfuric acid from the reaction medium during the purification of **2**. The infrared spectrum of **1** exhibited five characteristic broad absorption bands centered at 3366, 1624, 1384, 1045 and 555 cm^{-1} in close resemblance to those reported for fullerenols.[13]

The mass spectroscopic studies were carried out using the matrix-assisted laser desorption ionization (MALDI) technique with either sinapinic acid or 2,5-dihydroxybenzoic acid as a matrix material. As a result, the MALDI-MS spectrum of **1** (Fig. 2), derived from **2** prepared under a sulfation temperature of 70 °C for 12 h in the presence of oleum–P_2O_5, displayed a series of mass groups with a well-defined pattern of a nearly constant weight increase in 17 mass units at *m*/*z* (the mass of an ion fragmentation with a maximum peak intensity in each group) 738 ($n = 1$), 754 ($n = 2$), 771 ($n = 3$), 788 ($n = 4$), 806 ($n = 5$), 822 ($n = 6$), 839 ($n = 7$), 856 ($n = 8$), 873 ($n = 9$) and 890 ($n = 10$), except *m*/*z* 906 ($n = 11$) and 924 ($n = 12$) both of which had very low intensities. These ion fragmentations showing the gain of a hydroxy (OH) functional group to the preceding ion fragment agree well with the masses for the formula $C_{60}(OH)_n$; *i.e.* polyhydroxylated C_{60} derivatives. This clearly indicated the composition of the fullerenol molecule **1**, containing up to 12 hydroxy addends per C_{60} cage (dodecahydroxyfullerene).

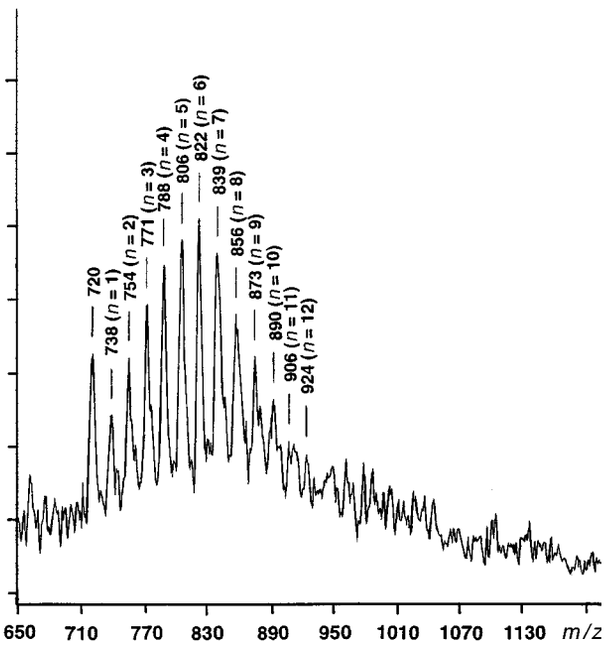


Fig. 2 Positive ion MALDI-MS spectrum of **1**, derived from **2** which was synthesized under a sulfation temperature of 70 °C for 12 h in the presence of oleum–P_2O_5, displaying a fragmentation pattern consistent with a mass of dodecahydroxylated fullerene

Experimental

Synthesis of hexacyclosulfated fullerene 2

A reaction flask (50 cm^3) charged with C_{60} (300 mg, 0.42 mmol) and fuming sulfuric acid (10 cm^3) was treated under ultrasonic conditions at 25 °C for 5 min. To the mixture was added P_2O_5 (800 mg, 5.6 mmol, 13 equiv.), then it was ultrasonicated for 5 min and then stirred at 60 °C under N_2 for 1.0 h to give a light brown solution with suspended bright orange microcrystalline solids. The resulting mixture was added dropwise into ice–water (60 cm^3) with vigorous stirring over an ice bath to effect complete precipitation of products. The precipitates were separated from solution by the centrifuge technique. They were then washed and centrifuged once with ice–water (20 cm^3) and twice with a mixture of cold diethyl ether and acetone (1 : 2, 30 cm^3 each), and dried in vacuum at 40 °C to afford orange–red solids of hexacyclosulfated fullerene **2** (450 mg); ν_{max}(KBr)/cm^{-1} 3421 (br), 2920w, 2450w (br), 1624w, 1427s (SO_2), 1235s (SO_2), 1168, 1051, 1002s, 979, 950s, 860, 841, 814, 801w, 775w, 640, 593, 531 and 513w, consistent with those reported previously[13] (Anal. Calcd. for $C_{60}H_{14}S_6O_{31}$ as $C_{60}(SO_4)_6 \cdot 7H_2O$: C, 50.63; H, 0.98; S, 13.50. Found: C, 49.50; H, 0.72; S, 12.20%). Incomplete combustion of **2** may have lead to the slightly lower than calculated values obtained.

Synthesis of dodecahydroxylated fullerene 1

A reaction flask (50 cm^3) equipped with a condenser and an inert gas bubbler was charged with hexacyclosulfated fullerene **2** (450 mg) and distilled water (10 cm^3). The mixture was stirred at 85 °C under N_2 for 10 h to give a dark brown suspension. The suspended solids were separated from aqueous solution by the centrifuge technique. They were washed and centrifuged twice with water and dried in vacuum at 40 °C to afford brown solids of dodecahydroxylated fullerene **1** (fullerenol, 355 mg, 84% overall yield from C_{60}); ν_{max}(KBr)/cm^{-1} 3366s (br, OH), 1624, 1384, 1045s, 555 and 526; *m*/*z* (MALDI-TOF-MS, positive ion, mass of the highest ion peak in the fragmentation group) 738 ($n = 1$), 754 ($n = 2$), 771 ($n = 3$), 788 ($n = 4$), 806 ($n = 5$), 822 ($n = 6$), 839 ($n = 7$), 856 ($n = 8$), 873 ($n = 9$), 890 ($n = 10$), 906 ($n = 11$) and 924 ($n = 12$) (Anal. Calcd. for $C_{60}H_{22}O_{17}$ as $C_{60}(OH)_{12} \cdot 5H_2O$: C, 71.00; H, 2.17; O, 26.82. Found: C, 71.28; H, 2.52; O, 26.20%). The product **1** is highly soluble in DMF and DMF–H_2O.

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16 A much slower sulfation rate of fullerenes at ambient temperatures was used to allow the kinetic detection of EPR resonances of the fullerenic radical intermediates.

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